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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 040283-0182

In re patent application of
David Reginald ADAMS et al.
Serial No. 09/600,631
Filed: February 12th, 2001
For: AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

Group Art Unit: 1626
Examiner: R. Anderson

DECLARATION UNDER 37 CFR § 1.132
OF NATHANIEL JULIUS MONCK

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Nathaniel Julius Monck, the undersigned, a citizen of Great Britain and a resident of Wokingham, United Kingdom, do hereby declare that:

1. I am one of the co-inventors of the invention described in the above-identified patent application entitled "AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS" which was given United States Serial No. 09/600,631, and accordingly I am familiar with the content of the present application.

2. I graduated as a Bachelor of Science from University of Bristol in 1990, and completed a Doctoral Degree from Imperial College, London University in 1993.

3. Since August 1996, I have been employed by VERNALIS RESEARCH LIMITED, assignee of the above-identified application, where I have been engaged in research and development of drugs useful in the treatment of CNS disorders, particularly anxiolytics.

4. I attach my Curriculum Vitae.

5. The elevated zero maze model described on pages 15 to 17 of the specification of United States Serial No. 09/600,631 is well recognized as a model for the assessment of anxiolytic or anxiogenic drug action, and therefore supports a claim to the method of treatment of anxiety. I attach hereto as an Appendix the abstracts of the following two papers

which demonstrate the significance of the elevated zero maze model in assessing drugs for anxiety treatment:

(i) *Behavioral and pharmacological characterization of the elevated "zero-maze" as an animal model of anxiety.* Shepherd, Jon K.; Greal, Savraj S.; Fletcher, Allan; Bill, David J.; Grewal, Savraj S. Department of Neuropharmacology, Wyeth Research (UK) Ltd., Berkshire, UK. Psychopharmacology (Berlin, Germany) (1994), 116(1), 56-64;

(ii) *Utility of ethological analysis to overcome locomotor confounds in elevated maze models of anxiety.* Weiss S M; Wadsworth G; Fletcher A; Dourish C T Cerebrus Limited, Winnersh, Wokingham, UK Neuroscience and biobehavioral reviews (1998), 23(2), 265-71.

6. The compounds exemplified in United States Serial No. 09/600,631 were tested in the elevated zero maze model and the result for Example 6 is given in the specification. A selection of the data collected for the other Examples is provided in Table 1 below, which shows the dosage (in mg/kg) of the compound for which a significant effect is observed in modulating the frequency of head dips.

Table 1

Example No	Effect in zero-maze test (dose, mg/kg)
7	45
8	30
10	100
14	100
15	30
17	10
18	10
36	30
51	10
53	30
55	30
56	10
58	30
60	10
66	10
68	30
70	30
71	30
83	30
84	30

The data in Table 1 show that the compounds of the present invention exhibit a significant anxiolytic effect.

7. I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 23rd March 2004

Nathaniel Julius Monck

U.S. Application No. 09/600,631

APPENDIX to

Declaration by Nathaniel Julius Monck on US Patent Application 09/600631

Supporting References for the significance of the zero-maze model in anxiety treatment

1. *Behavioral and pharmacological characterization of the elevated "zero-maze" as an animal model of anxiety*. Shepherd, Jon K.; Greal, Savraj S.; Fletcher, Allan; Bill, David J.; Grewal, Savraj S. Department of Neuropharmacology, Wyeth Research (UK) Ltd., Berkshire, UK. Psychopharmacology (Berlin, Germany) (1994), 116(1), 56-64. CODEN: PSCHDL ISSN: 0033-3158. Journal written in English. CAN 121:244935 AN 1994:644935 CAPLUS

Abstract

The elevated "zero-maze" is a modification of the elevated plus-maze model of anxiety in rats which incorporates both traditional and novel ethol. measures in the anal. of drug effects. The novel design comprises an elevated annular platform with two opposite enclosed quadrants and two open, removing any ambiguity in interpretation of time spent on the central square of the traditional design and allowing uninterrupted exploration. Using this model, the ref. benzodizepine anxiolytics diazepam (0.125-0.5 mg/kg) and chlordiazepoxide (0.5-2.0 mg/kg) significantly increased the percentage of time spent in the open quadrants (% TO) and the frequency of head dips over the edge of the platform (HDIPS), and reduced the frequency of stretched attend postures (SAP) from the closed to open quadrants. In contrast, the anxiogenic drug m-chlorophenylpiperazine (mCPP; 0.25-1.0 mg/kg) induced the opposite effects, decreasing % TO and HDIPS, and increasing SAP. The 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT; 0.001-0.1 mg/kg) had no effects on either % TO or HDIPS, but did decrease SAP at 0.01 mg/kg although not at higher or lower doses. Similarly, the 5-HT3 receptor antagonist, ondansetron (0.0001-1.0 mg/kg) decreased SAP and increased % TO at 0.01 mg/kg, but not at other doses. The present data suggest that a combination of the novel "zero-maze" design and a detailed ethol. anal. provides a sensitive model for the detection of anxiolytic/anxiogenic drug action.

2. *Utility of ethological analysis to overcome locomotor confounds in elevated maze models of anxiety.* Weiss S M; Wadsworth G; Fletcher A; Dourish C T Cerebrus Limited, Winnersh, Wokingham, UK Neuroscience and biobehavioral reviews (1998), 23(2), 265-71. Journal code: 7806090. ISSN:0149-7634. United States. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9884119 AN 1999098588 MEDLINE

Abstract

The elevated plus-maze is a commonly used model to identify putative anxiolytic and anxiogenic drugs. However, the validity of elevated plus-maze and other recently developed variants such as the elevated zero-maze has recently been questioned on the grounds that both the reference anxiolytic drug chlordiazepoxide and the psychostimulant d-amphetamine increase open arm exploration and stimulate locomotor activity. These findings suggest that measures of "anxiety" in the elevated maze cannot be adequately dissociated from simple changes in locomotor activity, which may confound the interpretation of results obtained using these models. A variety of approaches to assess drug effects on locomotor activity in the elevated maze have been suggested, including the use of total and closed arm entries, as well as supplementary tests such as exploration of the holeboard apparatus. However, all these approaches utilise the measurement of exploration in a novel environment, and as such, could potentially be influenced by either

changes in anxiety or locomotor activity. Recently, it has been shown that ethological measures of "risk assessment", such as stretched-attend postures and head-dipping, are sensitive indicators of drug-effects in the elevated maze. The present study assessed the utility of ethological analysis in dissociating locomotor activity from "anxiety" by comparing the effects of d-amphetamine to those of chlordiazepoxide in the rat elevated zero-maze. The results showed that both chlordiazepoxide and d-amphetamine increase the amount of time spent in the open arms and reduce "risk assessment" without increasing line crossing or rearing. These results confirm that under certain test conditions, psychostimulants are capable of producing "false-positives" in elevated maze models, and that both traditional methods and the ethological measures used in this study fail to unequivocally dissociate drug effects on anxiety from effects on locomotor activity. Further studies using other species and different classes of psychostimulants are warranted to determine the generality of these findings.

Nathaniel Julius Thomas Monck

10 Park Crescent, Sunningdale, Berkshire, SL5 0AX, UK.

Date of Birth: 16 July 1968

Professional Experience:

Aug 1996-present date	**Vernalis Research Ltd**, Winnersh Triangle. Principal Scientist, Chemistry Dept. Anxiety Project Leader (chemistry) 1997-2001 Sodium Channel Project Leader (chemistry) 2001-present date
Feb 1996-Aug 1996	**SmithKline Beecham**, Harlow. Industrial post-doctoral position. Synthesis of conformationally restricted unnatural amino-acids and incorporation into peptide mimetic libraries via combinatorial chemistry.
Feb 1995-Nov 1995	**The Australian National University**, Canberra, ACT. Post-Doctoral Research Fellow Research Advisor: Professor Lewis N. Mander, FRS Studies towards the total synthesis of gibberellic acid GA_{103}, the total synthesis of Harringtonolide and the partial synthesis of 7β-hydroxy-kaur-16-en-19-oic acid.
Jan 1994-Jan 1995	**The Ohio State University**, Columbus, Ohio. Post-Doctoral Research Fellow Research Advisor: Professor Leo A. Paquette Studies towards the total synthesis of Jatrophatrione.
Oct 1990-Dec 1993	**Imperial College**, University of London. Research Fellow; Research Advisor: Professor Steven V. Ley, FRS Development of new synthetic methods for the total synthesis of Milbemycin α_1 and Nemadectin β utilising relay studies of Nemadectin γ. Undergraduate Teaching Assistant; supervision and demonstration of laboratory experiments.
Oct 1992-Dec 1992	**Rhône-Poulenc-Rorer**, Dagenham. Research Fellow; Research Advisor: Dr Michael Ashton CASE award industrial placement.
Jul 1989-Aug 1989	**Institute of Child Health/Great Ormond Street Hospital**, London. Research Assistant; Research Advisor: P. Bird. Studies towards the development of HPLC methods for the analysis of samples from neofibroblastomer patients.

Awards/Honours:

1997-1998	MRSC CChem awarded as result of Structured Assessment.
1990-1993	CASE Award from Rhône-Poulenc-Rorer.

Courses:

Dec 1998	Introduction to Molecular Modelling, including the use of Legion, Selector, Flexidock and Gasp operations; Tripos Inc., Milton Keynes
July 1997	Medicinal Chemistry Residential Course: An introduction to the pharmaceutical industry. RSC, Canterbury.

Education:

1990-1993	Imperial College, University of London PhD, DIC, Synthetic Organic Chemistry Research Advisor: Professor Steven V. Ley, FRS Dissertation: Studies towards the Total Synthesis of the Milbemycins.
1987-1990	University of Bristol, Bachelor of Science (Hons), Chemistry, First class. Final year project supervisor: Dr Thomas V. Lee Dissertation: The Use of Enzymes in Organic Media.
1979-1986	Acland Burghley Comprehensive School, London A-levels: Chemistry (A), Mathematics (B), Physics (A) O-levels: French, History, Geography, Music, Chemistry, Physics, Mathematics, Advanced Mathematics, English Literature, English Language.

Bibliographic Information

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Preparation of azetidine carboxamides for the treatment of CNS disorders. Snape, Mike Frederick; Fletcher, Allan; Stanhope, Kelly Jean; Monck, Nathaniel Julius. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 39 pp. CODEN: PIXXD2 WO 0107043 A1 20010201.

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